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PERSPECTIVES

Rethinking Fluid Resuscitation in Septic Shock: A Phase-Adapted, Endothelium-Sparing Approach to Mitigate Capillary Leak

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Abstract: Sepsis-induced endothelial dysfunction and the resultant capillary leak syndrome are defining features of septic shock, posing a profound challenge to conventional fluid resuscitation strategies. The long-standing debate over crystalloid versus colloid administration is evolving beyond a simple dichotomy toward a more nuanced, physiologically informed approach. This review critically examines the pathophysiological cascade driving vascular hyperpermeability in sepsis—from endothelial glycocalyx degradation and inflammatory cytokine storms to oxidative stress and nitric oxide dysregulation. We trace the evolution of resuscitation paradigms from early goal-directed therapy to modern conservative approaches, highlighting the limitations of crystalloid-dominant protocols, including intravascular volume depletion despite a positive fluid balance and iatrogenic organ injury. Drawing on evidence from landmark clinical trials (eg, ALBIOS, CRISTAL, SMART) and a pharmacological reappraisal of fluid properties, we argue that a one-size-fits-all strategy is obsolete. Instead, this narrative review synthesizes recent trial evidence and pathophysiological insights to propose the Phase-Adapted, Endothelium-Sparing (PAES) resuscitation strategy, a novel framework that tailors fluid type and volume to the distinct temporal phases of septic shock: Rescue, Optimization, Stabilization, and De-escalation. This model advocates for initial resuscitation with balanced crystalloids, followed by the judicious integration of albumin in specific, high-risk patient subgroups to leverage its unique oncotic and pleiotropic, endothelium-stabilizing effects. We further outline how dynamic hemodynamic monitoring, point-of-care ultrasound, and emerging biomarkers of endothelial injury (eg, syndecan-1, angiopoietin-2) can guide the real-time implementation of this personalized strategy. The PAES framework aims to uncouple macrohemodynamic stabilization from microcirculatory injury, offering a pragmatic pathway to optimize perfusion, mitigate capillary leak, and improve outcomes in this critically ill population.

Keywords: personalized medicine, septic shock, fluid resuscitation, endothelial dysfunction, capillary leak syndrome

Introduction

Sepsis, a dysregulated host response to infection leading to life-threatening organ dysfunction, remains a leading cause of mortality and critical illness worldwide.[1] Its most severe manifestation, septic shock, is characterized by profound circulatory, cellular, and metabolic abnormalities. Central to this pathology is a catastrophic failure of the vascular endothelium.[2] The endothelium, far from being a passive conduit, is a dynamic organ that governs vascular tone, permeability, inflammation, and hemostasis.[3] In sepsis, it becomes the epicenter of a pathological cascade, resulting in widespread vasodilation, microcirculatory disruption, and a dramatic increase in vascular permeability—the so-called capillary leak syndrome.[4] This phenomenon leads to massive fluid shifts from the intravascular to the interstitial space, causing profound hypovolemia, tissue edema, and ultimately, multiple organ failure.[5,6]

For decades, fluid resuscitation has been the cornerstone of septic shock management, aimed at restoring intravascular volume and improving organ perfusion.[7] Yet, the optimal approach remains one of the most contentious topics in critical care medicine. The clinical paradigm has undergone a seismic shift, moving from the aggressive, protocolized "early

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goal-directed therapy" (EGDT) of the early 2000s to more conservative, individualized strategies following the publication of the landmark ProCESS, ARISE, and ProMISe trials.[8–11] This evolution reflects a growing recognition of a critical paradox: the very intervention designed to save lives—intravenous fluid—can itself propagate harm. Excessive fluid administration, particularly with crystalloids, contributes to a positive cumulative fluid balance, which is independently associated with increased mortality, prolonged mechanical ventilation, and acute kidney injury (AKI).[12,13]

The debate has traditionally been framed as a choice between crystalloids and colloids. Crystalloids are inexpensive and readily available, but their poor intravascular retention can exacerbate tissue edema.[14] Colloids, particularly albumin, offer superior oncotic pressure and prolonged intravascular residence, but concerns over the safety of synthetic colloids (eg, hydroxyethyl starch [HES]) and the cost of albumin have limited their universal adoption.[15,16] However, this simplistic "either/or" debate fails to address the underlying pathophysiology. The central challenge in septic shock resuscitation is not merely to fill the intravascular space, but to do so while actively protecting—or at least not further injuring—the fragile endothelial barrier.

Classically, septic shock has been understood primarily through the lens of macro-circulatory failure—characterized by profound vasoplegia and relative hypovolemia—and cellular metabolic dysexecution. While restoring macro-hemodynamic parameters remains the cornerstone of initial management, this macro-centric view often overlooks the barrier that mediates perfusion: the endothelium. This review challenges the conventional paradigm by reframing fluid resuscitation as a targeted pharmacological intervention. We argue that the choice of fluid, its volume, and its timing must be tailored to the dynamic pathophysiology of the septic endothelium. To this end, we critically synthesize the evidence on fluid pharmacodynamics and clinical outcomes to propose a novel, actionable framework: the *Phase-Adapted, Endothelium-Sparing (PAES)* resuscitation strategy. This strategy moves beyond a one-size-fits-all approach to align fluid therapy with the four distinct phases of shock management—Rescue, Optimization, Stabilization, and De-escalation. By strategically combining balanced crystalloids with the targeted use of albumin, and guiding therapy with advanced hemodynamic monitoring and biomarkers, the PAES framework provides a rational pathway to restore perfusion while mitigating capillary leak and iatrogenic fluid-related harm.

Search Strategy and Selection Criteria

For this narrative review, we conducted a systematic search of PubMed, Embase, and the Cochrane Library. The search strategy was executed in two phases: an initial broad search (from database inception to October 2025) to identify foundational literature on endothelial dysfunction and fluid resuscitation, followed by focused thematic searches prioritizing the period from January 2014 to October 2025. This timeframe was selected to capture contemporary evidence emerging after the publication of landmark sepsis trials.

We used combinations of medical subject headings terms and free-text keywords related to three core domains: Endothelial Pathophysiology (eg, "endothelial glycocalyx," "syndecan-1"); Pharmacology of Resuscitation Fluids (eg, "balanced crystalloids," "albumin," "ALBIOS," "SMART"); Clinical Management Strategies (eg, "fluid responsiveness," "deresuscitation"). We prioritized randomized controlled trials (RCTs), meta-analyses, and international guidelines published in English. The reference lists of retrieved articles were manually screened for additional relevant studies. A comprehensive description of the specific search strings and multi-stage methodology is provided in the Supplementary Material.

The Endothelium: The Epicenter of Septic Shock Pathophysiology

A sophisticated understanding of fluid therapy requires a deep appreciation for its primary target and principal casualty: the vascular endothelium. In sepsis, the endothelium transitions from a guardian of homeostasis to an active participant in a self-amplifying cycle of injury.[3,17]

Glycocalyx Degradation: The First Line of Defense Breached

The endothelial surface layer (ESL), a delicate gel-like mesh of proteoglycans (eg, syndecans, glypicans) and glycosaminoglycans (eg, heparan sulfate, hyaluronan), is the primary barrier regulating vascular permeability.[18] The glycocalyx acts as a molecular sieve, a mechanotransducer of shear stress, and a reservoir of antioxidants and anticoagulants.[19] Its

Table 1 Endothelial Glycocalyx Components and Their Dysregulation in Sepsis

Component	Physiological Function	Sepsis-Induced Alteration	Clinical Implication
Syndecan-1	Transmembrane proteoglycan; anchors heparan sulfate; mechanotransduction	Cleaved by MMPs and shed into circulation	Key biomarker for endothelial injury; correlates with mortality and fluid overload[28]
Heparan Sulfate	Binds antithrombin III, growth factors, and lipoproteins; regulates permeability	Degraded by heparanase; shed from syndecans[29]	Loss of anticoagulant properties (prothrombotic state); increased permeability
Hyaluronan	Provides hydration and viscoelasticity; contributes to barrier function	Fragmented by ROS; shed into circulation	Fragments are pro-inflammatory; promotes leukocyte adhesion[30]

Abbreviations: MMPs, matrix metalloproteinases; ROS, reactive oxygen species.

degradation is one of the earliest and most critical events in sepsis,[20] often occurring within hours of sepsis induction.[21] Inflammatory mediators, particularly tumor necrosis factor-alpha (TNF-α), and bacterial endotoxins trigger the release of enzymes like heparanase and matrix metalloproteinases (MMPs), which cleave core components of the glycocalyx from the endothelial surface.[22,23]

The shedding of these components into the circulation, such as syndecan-1 and hyaluronan fragments, serves as a quantifiable biomarker of endothelial injury and is strongly correlated with sepsis severity, organ dysfunction, and mortality.[21,24] The loss of the glycocalyx barrier dramatically increases vascular permeability, allowing plasma proteins and fluid to leak into the interstitium. This process not only causes tissue edema but also impairs microcirculatory flow by promoting leukocyte and platelet adhesion to the now-exposed endothelial cell surface.[25,26] Resuscitation itself can be a "second hit"; large volumes of crystalloids, especially unbalanced solutions like 0.9% saline, can further accelerate glycocalyx shedding through dilution of plasma proteins and direct inflammatory effects.[4,27] The consequences of this degradation are summarized in Table 1.

Inflammatory Cascade and Endothelial Apoptosis

The systemic inflammatory response in sepsis—often termed a "cytokine storm"—directly targets the endothelium. Pro-inflammatory cytokines like TNF-α and interleukin-6 (IL-6) induce profound changes in endothelial cells. They promote the upregulation of adhesion molecules (eg, E-selectin, ICAM-1), which facilitates neutrophil adhesion and transmigration, propagating inflammation within tissues.[31,32] Furthermore, these cytokines disrupt the integrity of inter-endothelial tight junctions by downregulating key structural proteins like VE-cadherin and claudin-5, creating paracellular gaps for fluid extravasation.[33]

The inflammatory milieu also pushes the endothelium toward a procoagulant state by inducing the expression of tissue factor and downregulating natural anticoagulants like thrombomodulin and protein C.[34,35] This contributes to the microthrombi formation and disseminated intravascular coagulation (DIC) often seen in severe sepsis. Finally, sustained inflammatory signaling can trigger programmed cell death (apoptosis) in endothelial cells, leading to denudation of the vascular lining and a complete loss of barrier function.[32,36]

Oxidative Stress and Nitric Oxide Dysregulation

Sepsis is a state of profound oxidative stress, where the production of reactive oxygen species (ROS) overwhelms the body's endogenous antioxidant defenses.[37,38] Activated neutrophils and endothelial cells themselves generate large amounts of superoxide via NADPH oxidase (NOX) enzymes. This excess ROS has multiple deleterious effects. It directly damages the glycocalyx, causes lipid peroxidation of cell membranes, and activates pro-inflammatory signaling pathways like nuclear factor-kappa B (NF-κB), perpetuating the inflammatory cycle.

Critically, ROS uncouples endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing the vasodilator nitric oxide (NO). Instead of producing NO, uncoupled eNOS generates more superoxide.[37] Simultaneously, inducible nitric oxide synthase (iNOS) is upregulated in response to inflammation, leading to a massive, uncontrolled surge in NO production. This "NO storm" is a primary driver of the profound vasodilation

and vasopressor-refractory hypotension characteristic of septic shock.[39,40] The excess NO also reacts with superoxide to form peroxynitrite, a highly potent oxidant that nitrates proteins, damages DNA, and causes mitochondrial dysfunction, further crippling endothelial cell function and promoting apoptosis (Figure 1).[37,38]

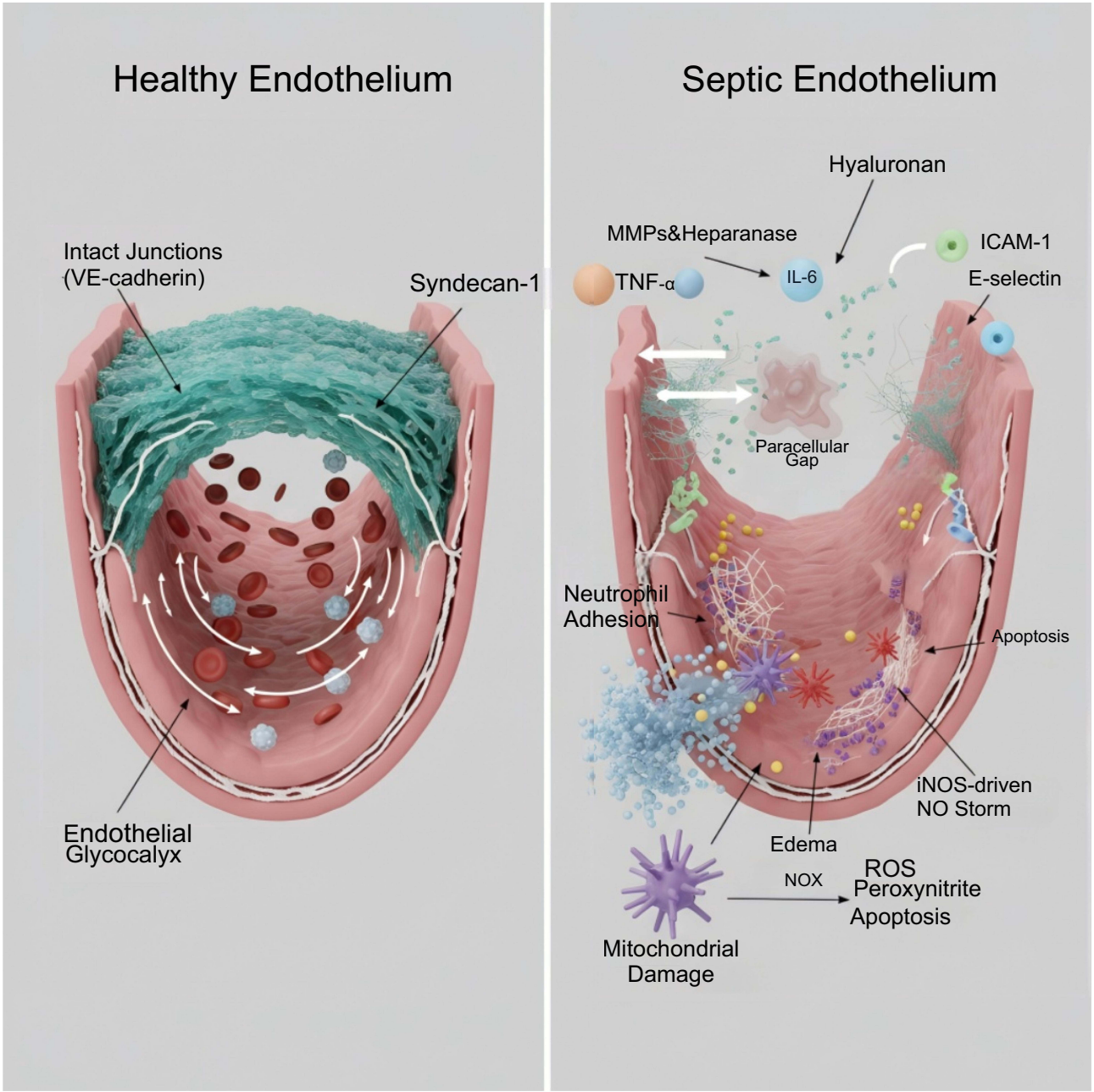

Figure 1 Pathophysiological Alterations of the Vascular Endothelium in Septic Shock. This infographic contrasts healthy endothelium with septic endothelium, illustrating key pathological changes. Healthy Endothelium: Shows intact endothelial cells with robust tight junctions (VE-cadherin) and a thick, continuous endothelial glycocalyx. Blood components flow smoothly in the lumen. Septic Endothelium: Depicts glycocalyx degradation (shedding Syndecan-1, Hyaluronan via MMPs, Heparanase), forming paracellular gaps, and causing vascular leakage (Plasma Proteins, Edema). Inflammatory triggers (TNF-α, IL-6) induce ICAM-1/E-selectin expression, promoting Neutrophil Adhesion and Endothelial Apoptosis. Oxidative stress (ROS from NOX) and iNOS-driven NO Storm lead to toxic Peroxynitrite ($ONOO^-$) formation, causing Mitochondrial Damage and further Apoptosis, culminating in endothelial barrier breakdown characteristic of septic shock.

From Aggressive Protocols to Individualized Care: The Evolution of a Paradigm

The approach to sepsis resuscitation has evolved significantly, reflecting a better understanding of the dangers of fluid overload. The era of rigid, aggressive protocols has given way to a more nuanced, conservative approach, as outlined in Table 2. This shift underscores the importance of individualizing therapy rather than adhering to uniform targets. Current guidelines reflect this evolving understanding but also highlight continuing areas of uncertainty. The 2021 Surviving Sepsis Campaign guidelines suggest using balanced crystalloids over saline and recommend albumin in patients requiring large volumes of crystalloids.[46] However, the guidelines also note there is insufficient evidence to recommend a strict restrictive versus liberal fluid strategy within the first 24 hours of resuscitation. Furthermore, the recommendation for albumin relies heavily on conditional benefits observed in subgroup analyses (eg, in septic shock) rather than definitive survival benefits in the broader sepsis population. This ongoing controversy regarding fluid volume limits and patient selection for albumin underlines the limitations of a standardized protocol and the necessity for a more personalized, phase-adapted approach.

A Pharmacological Reappraisal of Resuscitation Fluids

The choice of resuscitation fluid should be considered a pharmacological intervention with distinct mechanisms of action, pharmacokinetics, and adverse effect profiles. Understanding these differences is fundamental to developing an endothelium-sparing strategy.

Crystalloids: The Double-Edged Sword of Volume Expansion

Crystalloids are the first-line fluid for sepsis resuscitation globally.[7] Their primary advantage is the rapid expansion of the extracellular fluid compartment. However, their composition dictates their physiological impact.

Unbalanced Crystalloids (0.9% Saline): Isotonic saline has been the historical workhorse, but its supraphysiological chloride concentration (154 mmol/L) and acidic pH (~5.0–5.5) are increasingly recognized as harmful.[14,47] The high chloride load can induce a hyperchloremic metabolic acidosis, which has been linked to renal vasoconstriction, reduced glomerular filtration rate, and an increased incidence of AKI.[29,47] Studies have shown that saline administration is associated with more significant glycocalyx degradation compared to balanced solutions.

Balanced Crystalloids (eg, Lactated Ringer's, Plasma-Lyte): These solutions are formulated to more closely mimic the electrolyte composition of plasma, with lower chloride concentrations and the presence of a buffer (eg, lactate, acetate, gluconate) that is metabolized to bicarbonate.[48,49] The landmark SMART trial, which randomized over 15,000 critically ill adults, found that the use of balanced crystalloids resulted in a lower incidence of major adverse kidney events (MAKE) within 30 days (including death, new renal-replacement therapy, or persistent renal dysfunction) compared to saline.[50] A prespecified subgroup analysis of patients with sepsis in the SMART trial showed an even more pronounced benefit, with a significant reduction in 30-day mortality (25.2% vs 29.4%). By avoiding severe acid-

Table 2 Evolution of Fluid Resuscitation Paradigms in Sepsis Management

Parameter	Early Goal-Directed Therapy (EGDT, ~2001)	Modern Conservative Strategy (~2014 Onwards)
Fluid Volume	Aggressive early fluid administration (eg, 30 mL/kg boluses), often leading to volume overload	Titrated to response, often smaller aliquots (eg, 250–500 mL)[41,42]
Hemodynamic Targets	Static goals: CVP ≥8 mmHg, $ScvO_2$ ≥70%	Dynamic goals: Lactate clearance, perfusion markers (capillary refill time, mottling score), fluid responsiveness[43]
Vasopressor Initiation	Typically initiated after fluid resuscitation fails to achieve targets	Early norepinephrine if hypotensive, even during initial fluid challenges, to restore MAP and limit fluid[44,45]
Overall Philosophy	Protocolized, uniform approach to rapidly achieve predefined physiological targets	Individualized resuscitation, avoiding fluid overload, optimizing perfusion, and minimizing iatrogenic harm

Abbreviations: CVP, central venous pressure; ScvO, central venous oxygen saturation; MAP, mean arterial pressure.

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base disturbances and high chloride loads, balanced solutions appear to be a more physiologically sound and endothelium-friendly choice for initial resuscitation.

Despite these benefits, all crystalloids share a major pharmacokinetic limitation: rapid redistribution into the interstitial space. Only 20–30% of an infused crystalloid bolus remains in the intravascular compartment after one hour.[51] This poor volume-expanding efficiency means that large volumes are required to achieve hemodynamic targets, directly contributing to tissue edema, organ congestion, and the well-documented harms of a positive fluid balance (Table 3).

Colloids: From Synthetic Risks to Therapeutic Potential

Colloids contain large molecules that are retained in the intravascular space, exerting oncotic pressure to hold and draw fluid in.

Synthetic Colloids (HES, Gelatins): For years, synthetic colloids like HES were championed for their superior volume-expanding properties. However, a wealth of evidence has demonstrated significant harm. Multiple large RCTs (eg, 6S, CRISTAL) have consistently linked HES administration to an increased risk of AKI requiring renal replacement therapy and, in some studies, increased mortality in septic patients.[15,57] The mechanisms include direct renal tubular toxicity,[58] impaired coagulation,[59] and accumulation in tissues. Consequently, major regulatory bodies have issued strong warnings against their use in critically ill patients, effectively removing them from the therapeutic arsenal for sepsis.

Human Albumin: Albumin, the body's natural colloid, stands in stark contrast to its synthetic counterparts. It is responsible for 70–80% of plasma oncotic pressure and has a much longer intravascular half-life than crystalloids (Figure 2).[60] Beyond its oncotic function, albumin possesses remarkable pleiotropic properties that make it a uniquely attractive therapeutic agent in sepsis, as detailed in Table 4.

Clinical evidence for albumin remains heterogeneous and subject to ongoing debate. The landmark ALBIOS trial, which randomized 1,818 patients with severe sepsis to receive 20% albumin found no difference in 90-day mortality in the overall population (Table 5). This neutral primary outcome highlights that albumin is not a panacea for all sepsis phenotypes.

Although a prespecified subgroup analysis of patients with septic shock revealed a significant mortality benefit (43.6% vs 49.9%, $p = 0.03$), this finding represents secondary evidence and must be interpreted with caution.[65] The discrepancy between the strong physiological rationale and the mixed clinical results suggests the presence of competing mechanisms. In patients where shock is driven primarily by profound vasoplegia or cellular metabolic dysexecution (cytopathic hypoxia) rather than hypovolemia and capillary leak, albumin's oncotic benefits may be negligible.

Similarly, the recent ALPS trial in cirrhotic patients with sepsis-induced hypotension found no difference in 28-day mortality, reinforcing the lack of a universal survival benefit, although albumin did improve hemodynamics and lactate clearance.[66] Consequently, the PAES framework advocates for a targeted, rather than routine, use of albumin, specifically prioritizing it for the 'Optimization' phase in patients with refractory shock who are most likely to benefit from its oncotic and endothelial-protective properties.

Table 3 Comparative Pharmacokinetics and Physiological Effects of Crystalloid Solutions

Parameter	0.9% Saline	Balanced Crystalloids (eg, Lactated Ringer's)	Clinical Implication
Chloride Concentration	154 mmol/L (Supraphysiological)	98–110 mmol/L (Physiological)	Higher risk of hyperchloremic metabolic acidosis and renal injury with saline
pH	~5.0–5.5 (Acidic)	~6.5–7.4 (Physiological)	Balanced solutions help maintain physiological pH, reducing metabolic derangements
Intravascular Retention (1h)	20–30% of infused volume	35–40% of infused volume[52,53]	More rapid extravasation of saline exacerbates tissue edema and requires larger volumes
Glycocalyx Impact	Promotes glycocalyx shedding	Less glycocalyx degradation[54]	Balanced solutions may offer endothelial protection
Renal Effects	Reduced renal artery flow velocity; increased AKI risk[55]	Preserved medullary oxygenation; lower AKI incidence[56]	Superior renal outcomes with balanced solutions

Abbreviation: AKI, acute kidney injury.

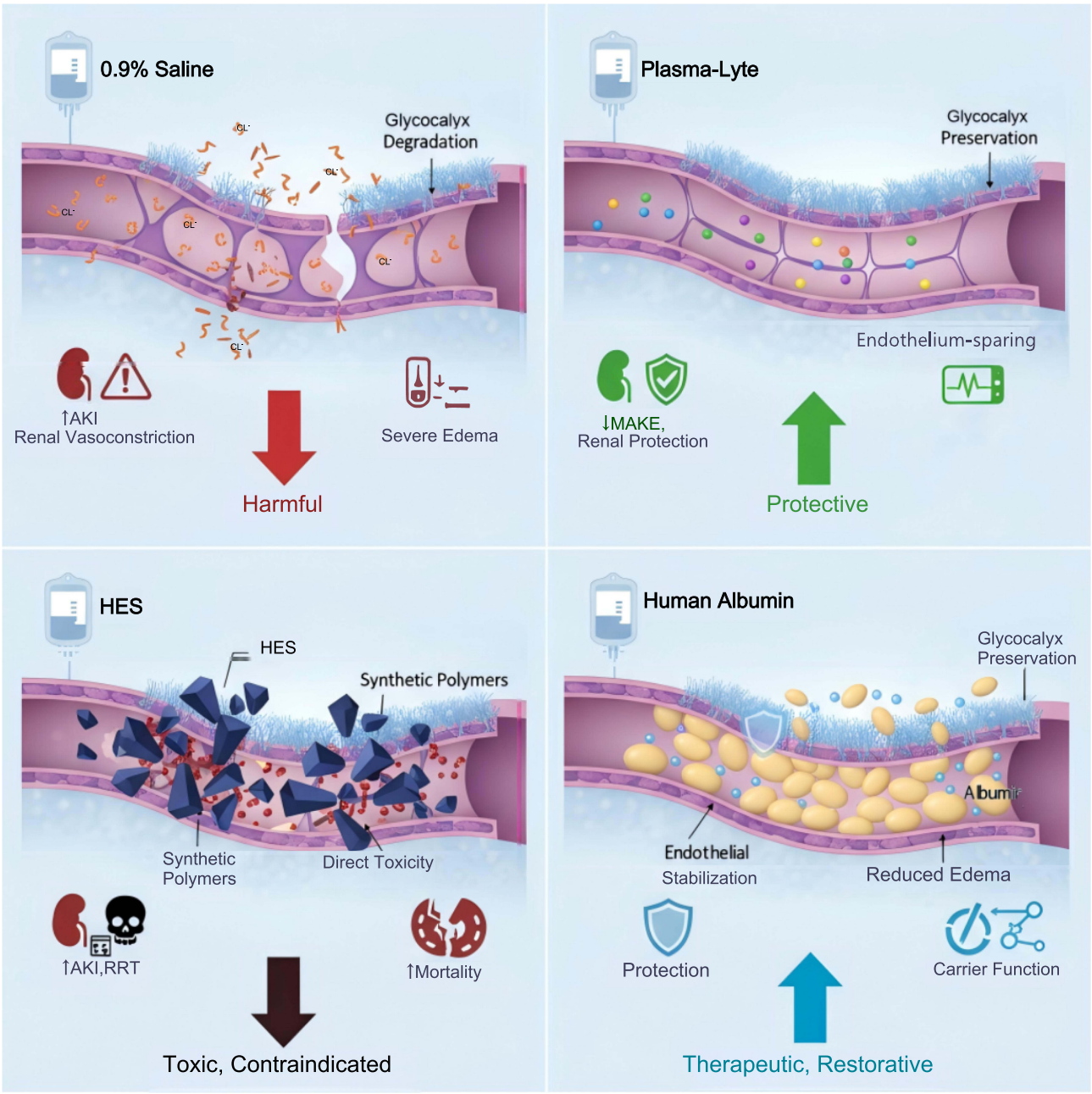

Figure 2 Conceptual Schematic of Fluid-Endothelium Interactions. This diagram illustrates the proposed mechanistic effects of resuscitation fluids on the endothelial glycocalyx. Unbalanced crystalloids (0.9% Saline) are depicted as promoting glycocalyx degradation, a mechanism linked in preclinical models to edema and renal injury. Balanced crystalloids support endothelial integrity, aligning with clinical data suggesting reduced renal risks. Synthetic colloids (HES) show direct toxicity and are contraindicated due to proven mortality risks. Human albumin is illustrated providing oncotic support and theoretical endothelial stabilization.
Notes: These depictions represent pathophysiological hypotheses. While the physiological rationale is strong, clinical benefits for albumin were primarily observed in septic shock subgroups rather than the overall population in landmark trials like ALBIOS.

Proposal: The Phase-Adapted, Endothelium-Sparing Resuscitation Strategy

The existing evidence compels a move away from a rigid, one-size-fits-all approach to a dynamic, physiologically-driven strategy. We propose the PAES framework, which aligns fluid therapy with the four recognized phases of sepsis resuscitation, integrating the best evidence for fluid choice, volume, and monitoring at each stage. This strategy builds on concepts of fluid responsiveness and deresuscitation, prioritizing endothelial health.

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Table 4 The Unique Pleiotropic Effects of Albumin in Sepsis

Mechanism	Pharmacological Effect	Relevance to Sepsis Pathophysiology
Oncotic Support	Provides ~75% of plasma oncotic pressure	Sustains intravascular volume with smaller infused volumes, reducing interstitial edema[61]
Endothelial Stabilization	Binds to glycocalyx; carrier for sphingosine-1-phosphate	Reinforces the endothelial barrier, directly counteracting capillary leak
Antioxidant Activity	Scavenges ROS via its free thiol group[36,62]	Mitigates the oxidative stress that drives endothelial cell damage and inflammation
Anti-inflammatory / Toxin Binding	Binds and neutralizes endotoxin, bilirubin, and nitric oxide[34,63]	Modulates the systemic inflammatory response and reduces vasodilation
Immune Modulation	Attenuates NF-κB activation; modulates macrophage responses[64]	Reduces pro-inflammatory cytokine release and tissue damage

Abbreviations: ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B.

Table 5 Summary of Landmark Fluid Trials in Sepsis and Critical Illness

Study (Design)	Population	Intervention	Primary Outcome	Secondary/Subgroup Findings	Evidence Context and Limitations
SMART (2018) (Pragmatic Cluster-Crossover RCT)	Critically ill adults (n=15,802)	Balanced Crystalloids vs Saline	Positive: Lower incidence of MAKE30 (14.3% vs 15.4%, p=0.04).	Mortality Signal: In-hospital mortality was lower in the sepsis subgroup (OR 0.88, p=0.01), though overall mortality was not statistically different (p=0.06).	Unblinded Design. Subjective outcomes (like RRT initiation) could be biased. The absolute risk reduction was small (~1.1%), requiring large numbers to treat (NNT ~91).
ALBIOS (2014) (Open-label RCT)	Severe sepsis/ septic shock (n=1,818)	20% Albumin (target ≥30 g/ L) vs Crystalloid alone	Neutral: No difference in 28-day mortality (31.8% vs 32.0%, p=0.39).	Shock Subgroup Signal: Significant mortality reduction in patients with septic shock (RR 0.87, p=0.03). Improved hemodynamic stability (lower fluid balance).	Post-hoc Subgroup Analysis. The survival benefit in shock was not the primary finding and requires prospective confirmation. Open-label nature may influence fluid administration.
CRISTAL (2013) (Open-label RCT)	Hypovolemic shock (mixed sepsis/ trauma) (n=2,857)	Colloids (HES, Gelatin, Dextran, Albumin) vs Crystalloids	Neutral: No difference in 28-day mortality (25.4% vs 27.0%, p=0.26).	Delayed Benefit: Significant reduction in 90-day mortality (30.7% vs 34.2%, p=0.03) favoring colloids. Less vasopressor/ ventilator days.	Heterogeneous Intervention. The Colloid group combined varying fluids (including HES and Gelatin), making it difficult to attribute benefits specifically to albumin versus others.
6S (2012) (Double-blind RCT)	Severe sepsis (n=798)	HES 130/0.42 vs Ringer's Acetate	Negative: Increased 90-day mortality (51% vs 43%, p=0.03) and increased risk of RRT (22% vs 16%).	N/A	Level I Evidence of Harm. High internal validity. Established that HES are toxic in sepsis, distinguishing them from natural colloids.
ALPS (2022) (Open-label RCT)	Cirrhosis with sepsis-induced hypotension (n=100 randomized)	20% Albumin vs Plasmalyte	Neutral: No significant difference in 28-day mortality (p=0.23, based on small sample).	Physiological Improvement: Albumin group achieved higher MAP and faster lactate clearance. Trend towards reduced need for dialysis.	Physiology ≠ Survival. Demonstrates that improved hemodynamics (higher MAP) does not automatically translate to survival benefit. Limited by small sample size.
BEST-Living (2024) (IPD Meta-analysis)	Critically ill adults (n=34,685)	Balanced Crystalloids vs Saline	High Probability of Benefit: Bayesian analysis showed >90% probability that balanced fluids reduce mortality.	Benefit appeared consistent across subgroups (sepsis, non-sepsis), with no significant subgroup interaction.	Moderate Certainty. While Bayesian probability is high, the frequentist analysis for mortality often crosses unity (OR ~0.96). Confirms balanced fluids as a standard.

Abbreviations: MAKE, major adverse kidney events; RCT, randomized controlled trial; NNT, number needed to treat; HES, hydroxyethyl starch; RRT, renal replacement therapy; MAP, mean arterial pressure; IPD, individual patient data.

Phase 1: Rescue (0–6 Hours)

The immediate goal is to reverse shock and restore perfusion to vital organs.[7] During this phase, patients exhibit significant vasodilation and hypovolemia.

Action: Initial resuscitation should begin with a bolus of balanced crystalloids (eg, 20–30 mL/kg), as recommended by the Surviving Sepsis Campaign. However, subsequent fluid should be administered in smaller, titrated boluses (eg, 250–500 mL) guided by frequent reassessment of fluid responsiveness using dynamic measures, not static pressures like central venous pressure (CVP).[41,67]

Rationale: Balanced crystalloids provide rapid volume expansion while mitigating the risks of hyperchloremic acidosis associated with saline.[50] Early and aggressive use of norepinephrine to maintain a mean arterial pressure (MAP) of ≥65 mmHg is crucial to restore vascular tone and limit the total volume of crystalloid required, preventing unnecessary fluid accumulation.

Phase 2: Optimization (6–24 Hours)

After the initial rescue, the goal shifts from rapid volume loading to carefully optimizing cardiac output and tissue perfusion while actively preventing fluid overload. Many patients will no longer be fluid responsive at this stage.

Action: Fluid administration should be restricted to patients who demonstrate clear evidence of fluid responsiveness. For these patients, titrated balanced crystalloids remain the primary choice. However, this is the critical phase to consider the integration of 20% albumin.[68,69] Albumin should be considered in patients with refractory shock requiring escalating vasopressor doses despite initial crystalloid resuscitation, those with documented severe hypoalbuminemia (<25 g/L), or those with emerging evidence of severe capillary leak (eg, high biomarker levels) or peripheral tissue hypoperfusion.[70,71]

Rationale: In this context, albumin is used not just as a volume expander but as a therapeutic agent to enhance vasopressor sensitivity, stabilize the endothelium, and sustain intravascular volume with a smaller fluid load, as suggested by the ALBIOS septic shock subgroup analysis and the ALPS trial. This "crystalloid-sparing" effect can help limit the accumulation of interstitial edema, and its pleiotropic effects contribute to microvascular integrity.[72]

Phase 3: Stabilization (24–72 Hours)

By this phase, the acute shock has typically resolved, but the patient remains critically ill with significant organ dysfunction and accumulated tissue edema from the initial resuscitation. The primary goal is to maintain a state of euvolemia.[73]

Action

All routine "maintenance" intravenous fluids should be ceased. Fluid administration should be limited to that required for medication delivery and enteral nutrition. The target is a neutral or zero cumulative fluid balance.[74]

Rationale

The focus shifts from "resuscitation" to "support." Preventing further fluid accumulation is paramount to allow for organ recovery, particularly of the kidneys and lungs. A persistent positive fluid balance in this phase is strongly associated with adverse outcomes, including increased mortality and prolonged mechanical ventilation.[12,13]

Phase 4: De-Escalation (>72 Hours)

This is the active fluid removal phase, often termed "deresuscitation." The goal is to achieve a negative fluid balance to mobilize interstitial edema and facilitate liberation from mechanical ventilation and other organ support.[75]

Action

This phase involves the judicious use of diuretics (eg, furosemide) in patients with adequate renal function or the initiation of renal replacement therapy with ultrafiltration in those with persistent AKI.[73,76]

Rationale

Mobilizing the "third-spaced" fluid reduces organ congestion, improves pulmonary compliance, and is associated with shorter intensive care unit (ICU) stays and improved survival.[13,41] Careful monitoring for hemodynamic tolerance to fluid removal is critical (Figure 3).

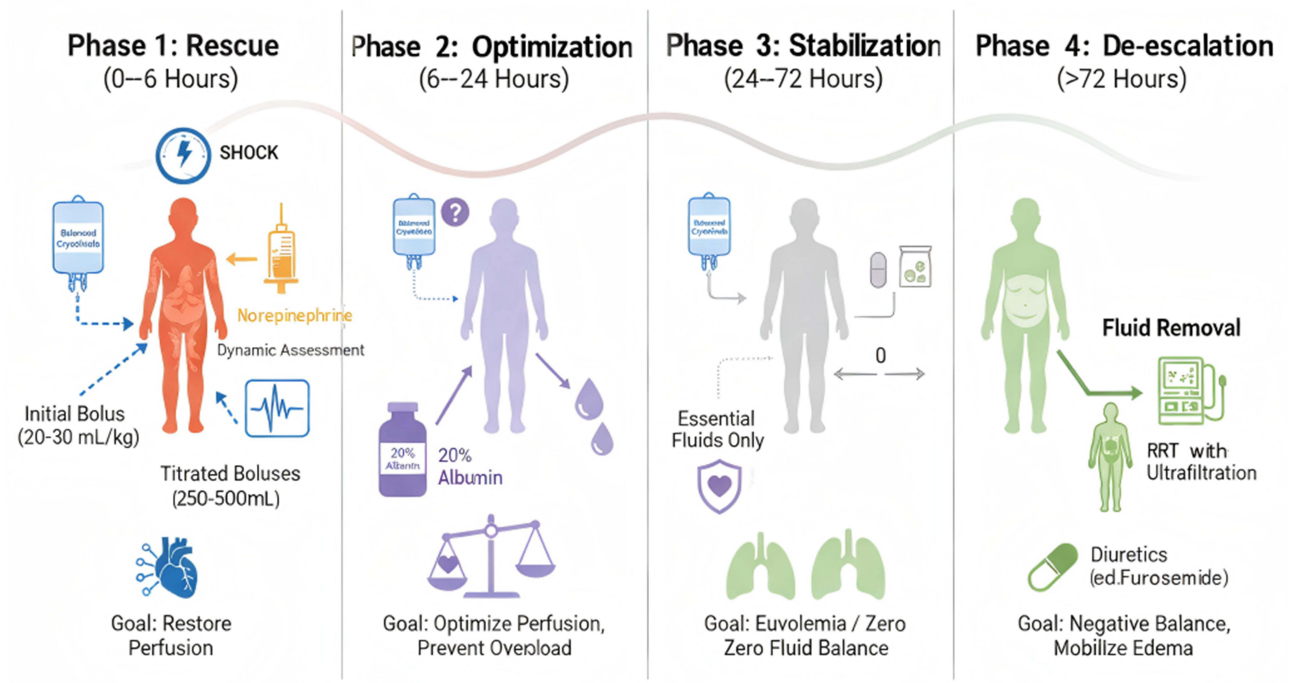

Figure 3 The Proposed Phase-Adapted, Endothelium-Sparing (PAES) Resuscitation Strategy. This diagram illustrates a conceptual framework tailoring fluid management to four phases. The Rescue phase (0–6 hours) prioritizes perfusion restoration with balanced crystalloids and early vasopressors. The Optimization phase (6–24 hours) aims to prevent overload, proposing the use of 20% albumin to potentially stabilize the endothelium in specific phenotypes. The Stabilization phase (24–72 hours) targets a zero fluid balance, while the De-escalation phase (>72 hours) focuses on active fluid removal via diuretics or ultrafiltration.
Notes: This algorithm integrates physiological principles with current evidence but represents a theoretical proposal for personalized care that requires prospective validation before routine implementation.

Guiding the PAES Strategy: The Role of Advanced Monitoring and Biomarkers

Implementing the PAES framework effectively requires moving beyond traditional static monitoring and embracing a modern, multimodal approach to assess the patient's fluid status and endothelial health in real time.

Dynamic Hemodynamic Assessment

Static measures like CVP are notoriously poor predictors of fluid responsiveness. Instead, dynamic assessments that evaluate the heart-lung interaction during mechanical ventilation (eg, stroke volume variation [SVV], pulse pressure variation [PPV]) or simulate a fluid bolus (eg, passive leg raise [PLR]) should be used to guide fluid decisions in the Rescue and Optimization phases.[45,67] A positive response (eg, >10–15% increase in stroke volume) indicates that the patient is on the steep part of their Frank-Starling curve and may benefit from further fluid. A negative response signals that further fluid is unlikely to improve cardiac output and will only increase the risk of overload.

Point-of-Care Ultrasound

Point-of-Care Ultrasound (POCUS) has become an indispensable tool at the bedside for guiding fluid therapy.

Fluid Responsiveness

Measurement of the inferior vena cava (IVC) diameter and its respiratory variation can help estimate right atrial pressure and predict fluid responsiveness.[77]

Fluid Tolerance

Lung ultrasound is highly sensitive for detecting interstitial edema (seen as "B-lines"). The appearance or worsening of B-lines is a strong signal of pulmonary congestion and a clear indication to stop fluid administration.[72]

Cardiac Function

A focused cardiac ultrasound can rapidly assess left and right ventricular function, identify pre-existing cardiac dysfunction that would predispose to fluid overload, and evaluate the heart's response to a fluid challenge. POCUS can reduce unnecessary fluid administration and improve adherence to conservative fluid strategies.[78]

Biomarkers of Endothelial Injury and Capillary Leak

The next frontier in personalizing fluid resuscitation is the integration of biomarkers that directly reflect the state of the endothelium.[79] Elevated circulating levels of syndecan-1 are a direct measure of glycocalyx degradation. Angiopoietin-2, a protein released from activated endothelial cells, is a key mediator of vascular destabilization and permeability.[80] High levels of these markers can identify patients with the most severe capillary leak and who might benefit most from endothelium-stabilizing therapies like albumin.[24,69] While not yet standard practice, these biomarkers hold immense promise for identifying patients at highest risk for harm from aggressive crystalloid resuscitation. Future clinical trials should aim to test biomarker-guided algorithms within the PAES framework.[81]

Capillary Refill Time

Capillary refill time (CRT) provides a real-time window into the microcirculation, shifting the resuscitation focus from abstract metabolic markers like lactate to tangible end-organ perfusion.[82] The landmark ANDROMEDA-SHOCK trial validated this approach, demonstrating that a CRT-targeted strategy reduced organ dysfunction and fluid administration compared to lactate-guided resuscitation. The subsequent ANDROMEDA-SHOCK-2 trial confirmed that a personalized hemodynamic protocol targeting CRT was superior to usual care for a hierarchical composite outcome, primarily by shortening the duration of vital support.[83,84]

Thus, CRT acts as both a titratable target during the Rescue and Optimization phases and, crucially, a physiological "stop signal" to prevent iatrogenic fluid overload, anchoring the entire framework in the patient's real-time microcirculatory status.

Limitations, Potential Risks, and Future Directions

The PAES framework offers a physiologically grounded approach to fluid resuscitation; however, several limitations and potential risks must be acknowledged before widespread implementation. First, the strategy relies heavily on accurate phase identification. Phase misclassification poses a significant safety risk: if a clinician incorrectly categorizes a patient in the "Rescue" phase as being in the "Optimization" phase, premature fluid restriction could exacerbate hypoperfusion and precipitate acute kidney injury. Conversely, aggressive deresuscitation in a patient with unresolved hemodynamic instability could lead to recurrent hypotension and organ ischemia.

Second, implementation failures may arise from the framework's reliance on advanced monitoring. The interpretation of fluid responsiveness and POCUS findings is operator-dependent, and variability in clinician expertise could lead to inconsistent application of the protocol. Finally, it is crucial to distinguish hypothesis from evidence. While individual components of PAES are supported by trials like SMART and ALBIOS, the integrated, multi-stage strategy itself remains a theoretical framework. It represents a proposal for personalization rather than a validated standard of care.

To bridge the gap between this theoretical framework and clinical practice, several key questions remain:

Prospective Validation

The PAES strategy, as a composite intervention, must be tested rigorously in large-scale randomized controlled trials against current standard care to demonstrate its safety and impact on patient-centered outcomes.

Biomarker-Guided Therapy

RCTs are needed to determine if a strategy of administering albumin based on specific biomarker thresholds (eg, syndecan-1 >40 ng/mL or angiopoietin-2 >12 ng/mL) improves outcomes compared to clinical judgment alone.[85]

Novel Endothelium-Protective Fluids

Research is ongoing into novel fluid formulations that combine volume support with active endothelial repair, such as those containing hyaluronan-based fluids or sphingosine-1-phosphate analogues. These preclinical candidates hold promise for directly targeting glycocalyx repair and reducing microvascular injury.[44,86,87]

The "Capillary Leak Index"

The development and validation of a composite score that integrates clinical signs of edema, POCUS findings, and multiple biomarkers could provide a more holistic and reliable measure of capillary integrity to guide therapy in real-time.[88]

Cost-Effectiveness in Resource-Limited Settings

While albumin shows promise, its high cost ($350/L versus $5/L for crystalloids) remains a significant barrier, especially in resource-limited settings.[89] Further research on cost-effectiveness and optimal implementation strategies in diverse healthcare environments is crucial.

Variability in Adherence to Protocols: Studies indicate significant variability in clinician adherence to nuanced fluid resuscitation protocols.[76] Development of robust educational programs and integration of decision-support systems are vital for successful implementation of strategies like PAES.[90]

Conclusion

Fluid resuscitation in septic shock is at a critical inflection point. The simplistic debate of crystalloids versus colloids is being replaced by a more sophisticated, physiologically-driven approach centered on the preservation of endothelial function. The PAES strategy offers a pragmatic and evidence-based framework to guide this modern approach. Operationally, this entails prioritizing initial resuscitation with balanced crystalloids, followed by the rational, targeted use of albumin in the optimization phase for the sickest patients, and concluding with dynamic assessment-guided active de-escalation. However, it is important to emphasize that while grounded in current physiological evidence, this framework requires rigorous prospective validation before it is adopted for widespread routine implementation. This strategy seeks to uncouple hemodynamic stabilization from iatrogenic harm. The integration of dynamic hemodynamic monitoring, point-of-care ultrasound, and emerging biomarkers will be essential to personalize this strategy at the bedside. By shifting our focus from merely filling a tank to actively protecting a fragile barrier, we can aspire to a future where fluid resuscitation is not only life-saving but also organ-sparing, ultimately improving the survival and quality of life for patients battling septic shock.

Abbreviations

PAES, Phase-Adapted, Endothelium-Sparing; EGDT, Early Goal-Directed Therapy; AKI, Acute Kidney Injury; HES, Hydroxyethyl Starch; TNF-α, Tumor Necrosis Factor-Alpha; MMPs, Matrix Metalloproteinases; ROS, Reactive Oxygen Species; ESL, Endothelial Surface Layer; IL-6, Interleukin-6; DIC, Disseminated Intravascular Coagulation; NOX, NADPH Oxidase; NF-κB, Nuclear Factor-Kappa B; eNOS, Endothelial Nitric Oxide Synthase; NO, Nitric Oxide; iNOS, Inducible Nitric Oxide Synthase; CVP, Central Venous Pressure; $ScvO_2$, Central Venous Oxygen Saturation; MAP, Mean Arterial Pressure; ICU, Intensive Care Unit; MAKE, Major Adverse Kidney Events; RCTs, Randomized Controlled Trials; IVC, Inferior Vena Cava; POCUS, Point-of-Care Ultrasound; SVV, Stroke Volume Variation; PPV, Pulse Pressure Variation; PLR, Passive Leg Raise; CRT, Capillary Refill Time.

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